Remarks/Arguments

Entry of the foregoing amendment is respectfully requested. No new matter is added by the amendment to the claims.

Claims 47-64 are pending in this application. Claims 47, 49, 50, 56, 58 and 59 have been amended in the present response, and no new matter has been added in the present response.

Applicants thank the Examiner for suggesting an update to the domestic priority statement to reflect that US application No. 10/374,539, filed February 25, 2003 is now U.S. Patent 6,784,205. Accordingly, the domestic priority statement has been updated.

Specification/Informalities

The Examiner noted that the application contained sequences that do not have sequence identifier. Accordingly, the specification has been amended to include the sequence identifiers.

Applicants enclose a substitute sequence listing which includes a sequence which was present in the specification but not in the original sequence listing. Applicants have amended the list of inventors in the substitute sequence listing to reflect the 1.48(b) Statement enclosed herewith.

The Examiner objected to Claims 47-50 and 56-59 as reciting "PTP-1B" and "TC-PTP" abbreviations without first reciting the entire phrase for which the abbreviation is used. Accordingly, the Claims have been amended to recite the phrases as noted.

The 35 U.S.C. 112, Second Paragraph, Rejection:

[a] Claims 47-64 were rejected under 35 U.S.C. 112, second paragraph, according to the Examiner as being indefinite for failing to particularly point out and

distinctly claim the subject matter which applicant regards as the invention. According to the Examiner, Claims 47-48, 49 and dependent Claims 52-55, Claim 50 and dependent Claim 51, Claims 56-57, 58 and dependent Claims 62-64, and Claim 59 and dependent Claims 60-61 are indefinite in the recitation of "PTP-1B" and "TC-PTP" as it is unclear from the claims and the specification as to the scope of the polypeptides that encompassed by the terms. The Examiner refers to paragraphs [0026] and [0027] of the specification and requested further clarification of the terms "PTP-1B" and "TC-PTP."

As noted in the above amended claims, PTP-1B represents protein tyrosine phosphatase 1B, and PTP-1B has been well described and characterized in the art by Elchebly *et al.* and Klaman *et al.* See paragraph [0026] of specification. Furthermore, the specification discloses a specific PTP-1B, which is human PTP-1B that is a 435 amino acid protein. The specification further states that for experimental studies of PTP-1B, the 298 amino acid form or a 321 amino acid form may be used because the full-length protein is insoluble in bacteria. The specification further teaches that "these truncated form are fully functional in activity and is consistent with the crystallographic findings that only the first 298 residues are ordered." See paragraph [0027], emphasis added. Furthermore, the specification teaches that "PTP-1B for the purposes of these methods is wild-type PTP-1B or any functional truncated form thereof (e.g., a form that is capable of dephosphorylating a phosphotyrosine and includes all of the native exosite-forming residues)." See paragraph [0043]. Accordingly, while the specification teaches that the truncated form of PTP-1B may be used, the disclosure clearly teaches that any PTP-1B, including without limitation the 298 amino acid form, the 321 amino acid form as well as the full length 435 amino acid form, are included within the scope of the term PTP-1B as long as there is functional activity associated with the PTP-1B protein.

Similarly, as noted in the above amended claims, "TC-PTP" represents T-cell protein tyrosine phosphatase, and TC-PTP has been well described and characterized in

the art. Furthermore, the specification discloses a specific TC-PTP that may be used for the method for finding compounds that bind to the exosite of TC-PTP and such TC-PTP include "the wild-type TC-PTP or any functional truncated form thereof (e.g., a form that is capable of dephosphorylating a phosphotyrosine and includes all of the native exosite-forming residues)." Non-exclusive examples of TC-PTP include human TC-PTP and the TC-PTP that comprises SEQ ID. NO:2. See paragraphs [0047] and [0048]. In addition, representative exosite mutants of TC-PTP with modified amino acid residues are disclosed in paragraphs [0049] to [0050]. Accordingly, the scope of the polypeptides that comprises the TC-PTP include a number of specific TC-PTP as disclosed in the specification, and include in part, forms of TC-PTP that has activity and is capable of dephosphorylating a phosphotyrosine.

In view of the explicit definitions and disclosure in the specification, Applicants respectfully assert that the terms "PTP-1B" and "TC-PTP" are clear, and Applicants respectfully request withdrawal of the 35 U.S.C. §112, second paragraph rejections of Claims 47-64.

[b] Claim 47 and dependent Claim 48, Claim 50 and dependent Claim 51, and Claim 56 and dependent Claim 57 were rejected as being indefinite because the recitation of the phrases "the exosite of PTP-1B", "the exosite mutant" or "the exosite of TC-PTP." According to the Examiner, the specification defines the "exosite" as a novel binding site that is distal to the active site of PTP-1B or TC-PTP, citing paragraphs [0018] and [0019]. Furthermore, the Examiner stated that the definition is not clear as to alternative binding site of PTP-1B and TC-PTP. In addition, the Examiner noted that there is insufficient antecedent basis for the limitation "the exosite of PTP-1B", "the exosite mutant" and "the exosite of TC-PTP" in the claims.

In addition to the definition for the exosite disclosed in paragraphs [0018] and [0019] as noted by the Examiner, the specification also teaches that, for example, for

PTP-1B, the "exosite is an adaptive binding site on PTPP-1B comprising at least one (preferably at least two residues) selected from the group consisting of: Glu-186; Ser-187; Pro-188; Ala-189; Leu-192; Asn-193; Phe-196; Lys-197; Arg-199; Glu-200; Leu-272; Glu-276; Gly-277; Lys-279; Phe-280; Ile-281; and Met-282." See paragraph [0030], page 7. Furthermore, the specification also teaches that for the PTP-1B exosite noted, "in the presence of a suitable ligand, one or more of these residues form an adaptive binding site that is not normally present." See paragraph [0030], and also illustrated in Figure 2. In addition, the specification teaches that the "exosite is referred to as an adaptive binding site because the presence of a suitable ligand induces major conformational rearrangement in the enzyme that creates the exosite binding site." See paragraph [0032]. As presently amended, there is now sufficient antecedent basis for the limitation "the exosite of PTP-1B", "the exosite mutant" and "the exosite of TC-PTP" in the Claims 49, 50, 58 and 59.

Accordingly, the term "exosite," as applied to the phrases "the exosite of PTP-1B", "the exosite mutant" or "the exosite of TC-PTP," is definite and the term is clearly illustrated with the description that the binding site that is distal to the active site, disclosed with a specific structure comprising a specific amino acid sequence, and defined as having, in part, a particular functional element-that induces major conformation rearrangement in the enzyme that creates the exosite binding site.

Applicants respectfully assert that the phrases "the exosite of PTP-1B", and similarly, "the exosite mutant" or "the exosite of TC-PTP" are definite, and withdrawal of the rejection is respectfully requested.

[c] Claims 47, 49 and dependent Claims 50-55, Claims 56, 58 and dependent Claims 59-64 were rejected as being indefinite in the recitation of "activity of PTP-1B" or "activity of TC-PTP" as it is unclear as to the "activity" that is intended as being

determined in the claimed methods. The Examiner suggested that the claims be identified by the intended "activity" that is being determined.

As amended, the above claims now recite that the activities of PTP-1B and TC-PTP correspond to their phosphatase activities. Support for the amendment is provided, for example, in paragraph [0020] and throughout the specification. Accordingly, Applicants respectfully assert that Claims 47, 49 and dependent Claims 50-55, Claims 56, 58 and dependent Claims 60-64, as amended, are definite. Withdrawal of the above indefinite rejections is requested.

[d] Claims 47 and dependent Claim 48, Claim 49 and dependent Claims 52-55, Claim 50 and dependent Claim 51, Claim 56 and dependent Claim 57, Claim 58 and dependent Claims 62-64, and Claim 59 and dependent Claims 60-61 were rejected according to the Examiner because "the claims are incomplete as the active method steps fail to achieve the desired result of identifying exosite inhibitors, particularly as it is unclear as to how a skilled artisan, by practicing the claimed methods, distinguishes an active site inhibitor of PTP-1B or TC-PTP from an "exosite" inhibitor of PTP-1B or TC-PTP." The Examiner further suggested that Applicants may incorporate a method step to distinguish an active site inhibitor of PTP-1B or TC-PTP from an exosite inhibitor of PTP-1B or TC-PTP. The Examiner suggested that method Claims 47, 49, 56 and 58 be amended to add the step of screening a test compound for potential exosite inhibition activity to distinguish test compounds that are active site inhibitors of PTP-1B or TC-PTP from compounds that are exosite inhibitors of PTP-1B or TC-PTP.

Applicants thank the Examiner for the above suggestion. However, Applicants note that it is within the scope of the above claims themselves, as recited, that constitute the screening methods for potential exosite inhibition activities that distinguish test compounds that are active site inhibitors of PTP-1B or TC-PTP from compounds that are

exosite inhibitors of PTP-1B or TC-PTP, and an additional method step as suggested by the Examiner is not required.

Support for the screening step is clearly provided in Example 7 (paragraphs [0113] to [0116]), where the examples describe a number of different screening methods for potential exosite inhibitors. According to one described procedure of the screening method in Example 7, the "assays are used to distinguish between true exosite inhibitors form those compounds that inhibit through non-specific interaction." The procedure describes the use of a test compound ("a candidate") for "an exosite inhibitor using a range of enzyme concentrations that is capable of allosteric regulation (referred herein as the catalytic competent enzyme). If the compound is inhibiting solely through the allosteric mechanism, then the observed inhibition should be predictable." And the inhibition of the enzyme may be calculated using the equation provided in Example 7. According to the method, true exosite inhibitors may be determined by changing the enzyme concentration and observing the rate of inhibition, and therefore, by employing the disclosed procedure, there is no need to employ the additional step of comparing the activity of a test compound with the activity of an exosite mutant of the protein in the presence of the test compound.

Paragraph [0116] of the specification provides additional methods for identifying an exosite inhibitor of a protein by contacting the exosite of the protein with a test compound and determining the activity of the protein with the test compound in the absence of the comparison step for the activity of a test compound with the activity of an exosite mutant of the protein in the presence of the test compound.

Accordingly, Claim 49 as amended, recites the method of identifying an exosite inhibitor comprising contacting a test compound with PTP-1B having phsophatase activity and having specific amino acid(s), and further, the step of determining the inhibition activity with the test compound. Similarly, as applied to independent Claim 56

(and its dependent claims) for the method of identifying an exosite inhibitor of TC-PTP, the claimed method is complete and provides definitive instructions for a skilled artisan to practice the claimed methods.

Applicants respectfully assert that independent method Claims 47, 49, 56 and 58 are complete and definite, and clearly recite the method for identifying exosite inhibitors of PTP-1B and TC-PTP. Withdrawal of the rejection is respectfully requested.

[e] Claims 49, 54-55, 58 and 62-64 were rejected as being indefinite for recitation of specific amino acid positions without reciting a reference sequence. The Examiner suggested the addition of sequence identifiers. Applicants respectfully traverse the Examiner's alleged procedural requirement for reciting specific reference sequence identifiers for well known peptide compositions and/or their variants in a claim when the claim recite one or more specific amino acid residue positions.

As stated in Section **[a]** above, Applicants note that PTP-1B has been well described and characterized in the art by Elchebly *et al.* and Klaman *et al.* and the specification discloses, for example among others, human PTP-1B that is a 435 amino acid protein. The specification further discloses a 298 amino acid form, a 321 amino acid form, wild-type and various truncated forms of PTP-1B having functional activities may be used in experimental procedures.

Similarly, TC-PTP has been well described and characterized in the art, and the specification discloses a specific TC-PTP that may include the wild-type TC-PTP or any functional truncated forms thereof. Explicit, non-exclusive examples of TC-PTP include human TC-PTP, the TC-PTP that comprises SEQ ID NO:2, and representative exosite mutants of TC-PTP with modified amino acid residues are disclosed in paragraphs [0049] to [0050].

Accordingly, Applicants respectfully assert that Claims 49, 54-55, 58 and 62-64 are not indefinite because the compositions are well known in the art and clearly

disclosed in the specification, and Applicants are unaware of any procedural requirements for inserting any particular sequence identifier for molecules with well known compositions even when the claims recite a specific amino acid position. The Examiner is respectfully requested to quote the rules in support of the rejection. Otherwise, withdrawal of the indefinite rejection of Claims 49, 54-55, 58 and 62-64 is respectfully requested.

[f] Claim 59 was rejected as being confusing because Claim 59 depends on Claim 58 that refers to "TC-PTP" while Claim 59 recite "PTP-1B." Applicants thank the Examiner for noting the typographical error.

Claim 59 has been amended to correct the typographical error; and the Examiner is requested to withdraw the rejection.

The 35 U.S.C. 112, First Paragraph, Rejection:

[11] Claims 47-64 were rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. According to the Examiner, the claims are drawn to methods of using a genus of "PTP-1B" or "TC-PTP" polypetides and exosite mutants thereof. The Examiner cited UC California v. Eli Lilly (43 USPQ2d 1398) for the proposition that claims to a chemical genus requires "a description of a chemical species, 'requires a precise definition, such as by structure, formula [or] chemical name,' of the claimed subject matter sufficient to distinguish it from other materials." Furthermore, for claims to a genus, "MPEP § 2163 states the written description requirement for a claimed genus may be satisfied through sufficient description of a representative number of species by actual reduction to practice, reduction to drawings, or by disclosure of relevant identifying characteristics, *i.e.*, structures or other physical and/or chemical properties, by functional characteristics coupled with a known or disclosed correlation between function and structure, or by a combination of such identifying characteristics, sufficient to show the applicant was in

possession of the claimed genus. MPEP § 2163 states that a representative number of species means that the species which are adequately described are representative of the entire genus. Thus, when there is substantial variation within the genus, one must describe a sufficient variety of species to reflect the variation within the genus."

The Examiner alleges that the specification discloses only a single representative species of the genus of PTP-1B polypeptides, *i.e.*, SEQ ID NO:1, only a single representative species of the genus TC-PTP polypetides, *i.e.*, SEQ ID NO:2, and only 17 residues of an "exosite" wherein mutations may be made to either of SEQ ID NO:1 or 2. Accordingly, the Examiner notes that the specification fails to describe any additional species by any relevant, identifying characteristics or properties other than being "PTP-1B" or "TC-PTP" polypeptides or exosite mutants thereof. The Examiner further alleges that the recitation of "PTP-1B" or "TC-PTP" fails to provide a sufficient description of the recited genus of proteins as it merely describes the "functional" features without providing any definition of the structural features of the species within the genus. The Examiner cited the *UC California v. Eli Lilly* case in which the CAFC determined that 'vertebrate insulin cDNA' or 'mammalian insulin cDNA" without more, is not an adequate written description of the genus because it does not distinguish the claimed genus from others, except by function. And the Examiner concludes that the specification fails to sufficiently describe the claimed invention in such full, clear, concise, and exact terms that a skilled artisan would recognize that Applicants were in possession of the claimed invention.

Applicants respectfully traverse the Examiner's characterization of the specification, claims and the conclusions drawn from these mis-characterization of the claims in view of the scope of the disclosure. First, Applicants note that the term "PTP-1B", as noted in Section **[a]** above, is well known in the art, and is an extensively studied protein tyrosine phosphatase. As noted in paragraph [0021] of the specification, the

signature motif of a PTP has also been described and characterized as being found, in part, "in a critical loop ... in the active site of the catalytic PTP domain and includes two (cysteine and arginine) of the three essential catalytic residues," and that "the third catalytic residue is aspartic acid and is found in the WPD loop", as described by Zhang (2001) and Zhang (2002). Furthermore, the specification discloses that "all PTPs are characterized by their ability to hydrolyze p-nitrophenyl phosphate without the presence of a metal ion, sensitivity to vanadate, and insensitivity to okadaic acid." In addition, the specification describes that the structure of the PTP domain has been solved and characterized (paragraph [0022]) and the active site of the PTP domain is well characterized as being "located within a crevice on the molecular surface and is formed by several critical loops (see paragraph [0023). Accordingly, it is apparent that the structure of PTP is taught with clarity and specificity. Paragraph [0024] of the specification further describes the function of PTP by way of the mechanism for the hydrolysis reaction by PTPs in great detail.

The specification also discloses that human PTP-1B is a 435 amino acid protein having a known sequence. In addition, the specification discloses the truncated forms having 298 amino acids and a 321 amino acid form. See paragraph [0027]. The specification also discloses at least 17 specific amino acid residues for the adaptive binding site for PTP-1B "comprising at least (more preferably at least two residues) selected form the group consisting of Glu-186; Ser-187; Pro-188; Ala-189; Leu-192; Asn-193; Phe-196; Lys-197; Arg-199; Glu-200; Met-272; Glu-276; Gly-277; Lys-279; Cys-280; Ile-281; and Lys-282." Accordingly, for a particular PTP-1B having one particular amino acid listed above, there are 17 different PTP-1B variants. However, where there are "at least two residues" from the above list, there is described at least another 10 different PTP-1B variants, etc ... Accordingly, based on the above description in

paragraph alone, the specification teaches at least one hundred different specific structural permutations of PTP-1B.

Similarly, the specification also discloses specific amino acids for the TC-PTP exosite-forming residues as comprising Glu-186; Ser-187; Pro-188; Ala-189; Leu-192; Asn-193; Phe-196; Lys-197; Arg-199; Glu-200; Met-272; Glu-276; Gly-277; Lys-279; Cys-280; Ile-281; and Lys-282. See paragraph [0037]. Accordingly, the specification describe with particularity, at least another several dozens (or hundreds) possible permutations for different TC-PTP compositions. The sequence alignment of PTP-1B and TC-PTP are also provided to demonstrate sequence identity of the two proteins. See paragraph [0029].

Paragraph [0038] of the specification teaches the specific interactions of an exosite-forming residue with a compound that may form "a hydrogen bond, a salt bridge, or a van der Waals contact with an exosite forming residue." Paragraphs [0038] to [0040] further discloses the distance parameters for forming hydrogen bonds for amide-carbonyl, amide-hydroxyl, or amide-imidazole groups, for forming salt bridges, and for forming van der Waals interactions.

Accordingly, Applicants respectfully assert that the specification provides a large number of exemplified structural description of the genus of PTPs, and also provides functional description, features and properties of the genus of PTPs, including a number of PTP-1B and TC-PTP polypeptides species in great detail and specificity, as noted above, that a skilled artisan would recognize that Applicants were in possession of the claimed invention.

The Examiner is respectfully requested to withdraw the 35 U.S.C. 112, first paragraph, rejections of Claims 47-64.

[12] Claims 47-64 were rejected under 35 U.S.C. 112, first paragraph, because "the specification, while being enabling for a method for identifying an exosite inhibitor

of PTP-1B of SEQ ID NO:1 or TC-PTP of SEQ ID NO:2 comprising the steps of 1) contacting SEQ ID NO:1 or 2 with a test compound and a substrate, 2) contacting an exosite mutant as disclosed at pp. 28-29, paragraphs [0108] to [0111] of the specification with said test compound and said substrate, wherein said exosite mutant has PTP activity, and 3) comparing the phosphatase activity of SEQ ID NO:1 or 2 in the presence and absence of said test compound, etc ..., does not reasonably provide enablement for all methods for identifying an exosite inhibitor as encompassed by the claims. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims." The Examiner then cites the factors summarized in *In re Wands* (858 F.2d 731, 8 USPQ2d 1400 (Fed. Cir. 1988) and discussed the factors in detail.

Applicants respectfully traverse the Examiner's rejections, summarizing the *In re Wands* factors, and respond to the Examiner as noted below.

Enablement: The Legal Standard

When making a rejection on the ground of alleged lack of enablement, the Examiner has the "initial burden of setting forth a reasonable explanation as to why [he/she] believes that the scope of protection provided by [the] claim is not adequately enabled by the description of the invention provided in the specification." *In re Wright*, 999 F.2d 1557, 1562, 27 USPQ2d 1510, 1513 (Fed. Cir. 1993). Without a reason to doubt the truth of the statements made in the patent application, the application must be considered enabling. *In re Wright, supra*; *In re Marzocchi*, 439 F.2d 220, 223, 169 USPQ 367, 369 (CCPA 1971).

The test for enablement entails an analysis of whether one skilled in the art would have been able at the effective filing date to practice the invention using information

disclosed in the application and information known in the art without undue or unreasonable experimentation (MPEP § 2164.01; see In *re Wands,* 858 F.2d 731, 8 USPQ 2d 1400, [Fed. Cir. 1988]). A finding of lack of enablement and determination that undue experimentation is necessary requires an analysis of a variety of factors *(i.e.,* the *In re Wands* factors). The most important factors that must be considered in this case include 1) the nature of the invention; 2) the level of ordinary skill in the art; 3) guidance provided in the specification; and 4) the state of the prior art. "[H]ow a teaching is set forth, by specific example or broad terminology, is not important"; and furthermore still, "limitations and examples in the specification do not generally limit what is covered by the claims" (MPEP § 2164.08). The determination of what constitutes undue experimentation in a given case requires the application of a standard of reasonableness, having due regard for the nature of the invention and the state of the art. *Ansul Co. v. Uniroyal, Inc.* 448 F.2d 872, 878-79; 169 USPQ 759, 762-63 (2d Cir. 1971), cert. denied, 404 U.S. 1018, 30 L. Ed. 2d 666, 92 S.Ct. 680 (1972). The test is not merely quantitative, since a considerable amount of experimentation is permissible, if it is merely routine, or if the specification in question provides a reasonable amount of guidance with respect to the direction in which the experimentation should proceed. It is well settled that patent applicants are not required to disclose every species encompassed by their claims, even in an unpredictable art. The legal standard merely requires that there must be sufficient disclosure, either through illustrative examples or terminology, to teach those of ordinary skill how to make and use the invention as broadly as it is claimed. *Enzo Biochem., Inc. v. Calgene, Inc.,* 188 F.3d 1362 (Fed. Circ. 1999), at 1372 (quoting *In re* Vaeck, 947 F.2d 488, 496 (Fed. Cir. 1991)).

Proper application of the legal standard

Proper application of the legal standard must lead to the conclusion that Claims 47-64 pending in this application are fully enabled.

The Claimed Invention:

The present invention is from the field of designing new and improved methods for treating diabetes and/or its associated complications by modulating the activity of protein tyrosine phosphatase 1B ("PTP-1B"). In particular, the application discloses, in part, methods for identifying exosite inhibitors of PTP-1B and exosite inhibitors of TC-PTP. At the time the present invention was made, as noted in Section **[a]** above, there was extensive information known in the art relating to PTP-1B and TC-PTP protein tyrosine phosphatases and their structures. Standard methods for the preparation and testing of biologically active compounds have been extensively reported in the literature, and are exemplified in the present application on pages 14-43. Accordingly, although unpredictability in the field of designing methods for identifying inhibitor compounds for PTP-1B and TC-PTP protein tyrosine phosphatases may be viewed as relatively high, the unpredictability in the particular field to which the present invention as taught in the present application is of a lesser degree.

The breadth of the claims: According to the Examiner, "the claims are so broad as to encompass the use of any PTP-1B or TC-PTP polypeptide and "exosite mutant" thereof." The Examiner alleges that the specification defines an "exosite mutant" in a limited way, and that there is "no indication in the specification that the "exosite mutant" necessarily maintains phosphatase activity. Thus, the "exosite mutant" can be catalytically inactive."

First, Applicants emphasize that the claims recite a method for identifying an exosite inhibitor using PTP proteins, and the specification clearly teaches the various PTP-1B and TC-PTP polypeptides species in great detail and specificity, such that a skilled artisan would recognize that Applicants were in possession of the claimed invention. The claimed method does not rely on heretofore generally unknown or undescribed research methods or techniques.

As the CCPA stated in *In re Marzocchi*, 169 USPQ 367, 370 (CCPA 1971), "A specification disclosure that contains a teaching of the manner and process of making and using an invention in terms which correspond in scope to those used in describing and defining the subject matter sought to be patented must be taken as being in compliance with the enablement requirement of 35 U.S.C. 112, first paragraph, unless there is a reason to doubt the objective truth of the statements contained therein which must be relied upon for enabling support." And "it is incumbent upon the Patent Office, whenever a rejection on this basis is made, to explain *why* it doubts the truth or accuracy of any statement in a supporting disclosure and to back up assertions of its own with acceptable evidence or reasoning which is inconsistent with the contested statement. Otherwise, there would be no need for the applicant to go to the trouble and expense of supporting his presumably accurate disclosure."

Second, in contrast to the Examiner's statement that an "exosite mutant" is defined as having "at least one of the ... exosite –forming residues ... modified to a different amino acid such that the resulting [polypeptide] is no longer capable of being inhibited through the exosite or displays a diminished capacity ... of being inhibited through exosite" (quoting page 12, paragraph [0044] and page 13, paragraph [0049]), and that "the "exosite mutant" can be catalytically inactive." See page 11 of Office Action. Applicants note that it is only a partial definition as quoted by the Examiner. The specification defines an "exosite mutant of TC-PTP" as a "TC-PTP wherein at least one of the TC-PTP exosite-forming residues has been modified to a different amino acid such that the resulting TC-PTP is no longer capable of being inhibited through the exosite site or displays a diminished capacity (less than about 75% inhibition compared to SEQ ID NO. 2 for a known exosite inhibitor such as compound **5**; preferably less than about 50%, more preferably less than about 25%) of being inhibited through the exosite." See paragraph [0049]. Accordingly, there is no reason to conclude from the specification that

"the 'exosite mutant' can be catalytically inactive" as suggested by the Examiner. As noted with the legal standard above, [w]ithout a reason to doubt the truth of the statements made in the patent application, the application must be considered enabling. *In re Wright, supra.*

As noted in Applicants comments in Section **[11]** above, the specification teaches at least one hundred different specific structural permutations of PTP-1B and a large number of TC-PTP that may be employed in the method of the invention. Accordingly, Applicants assert that the Examples noted above provide a sufficient disclosure with illustrative and specific procedures to enable one skilled in the art to make and use the invention commensurate with the scope of the claims. That is, the scope of the disclosure of the specification having specific examples enables the scope of the claims. And the Examiner has not provided a reason why the disclosure would not enable the invention commensurate with the scope of the claims.

The state of the prior art; The level of one of ordinary skill in the art; and The level of predictability: According to the Examiner, "at the time of the invention, recombinant wild-type human PTP-1B and recombinant human TC-PTP polypeptide and methods for identifying active-site inhibitors thereof were known in the art as evidenced by Wrobel et al. (*J. Biol. Chem. 276*:26036-26043). However, the effects of altering the sequences of these polypeptides was highly unpredictable. ... The position within a protein's sequence where modifications can be made with a reasonable expectation of success in obtaining a polypeptide having the desired activity/utility are limited in any protein and the result of such modification is highly unpredictable." The Examiner further cites the reference Branden *et al.* ("Introduction to Protein Structure", Garland Publishing Inc., New York, 1991) and notes that Branden "teaches '[p]rotein engineers frequently have been surprised by the range of effects caused by single mutations that they hoped would change only one specific and simple property in enzymes" and "[t]he

often surprising results of such experiments reveal how little we know about the rules of protein stability ... they also serve to emphasize how difficult it is to design *de novo* stable proteins with specific functions" (page 247). The Examiner further supports the notion of unpredictability, quoting the reference of "Wikowski *et al.* (*Biochemistry 38*:11643-11650), which teaches that only a single amino acid substitution results in conversion of the parent polypeptide's activity from a beta-ketoacyl synthase to a malonyl decarboxylase (see *e.g.*, Table 1, page 11647)."

The State of the Prior Art: As discussed on page 4 of the specification, PTP-1B and TC-PTP are protein tyrosine phosphatases, the signature motif of a PTP has been disclosed by Zhang *et al* as being found in a critical loop, and all PTP are characterized by their ability to hydrolyze p-nitrophenyl phosphate. In addition, there are known drug programs targeting PTP-1B and TC-PTP that have focused on identifying active site inhibitors, and have succeeded in identifying potent active site inhibitors against target enzymes. See paragraph [0025].

The level of one of ordinary skill in the art: It is well established that the level of skill in this technology is relatively high, and is typically represented by the knowledge of a master scientist or a Ph.D. scientist with several years of experience in the field of genetic engineering, biochemistry and chemistry.

The level of predictability: While Applicants do not dispute the statements of Branden *et al* or the quotation of Witkowski *et al*, with respect to the potential effects of a single site mutation to a protein's structure or function, as quoted by the Examiner. However, at the time the present invention was made, there was extensive information known in the art relating to various methods for the modification of proteins, and methods for single or multiple mutation of polypeptides and proteins, including for example, the methods cited in the Branden *et al* and the Witkoswski *et al* references, cited by the Examiner. Thus, although, as the Examiner notes on page 12 of the Office Action, there

might exist a certain level of unpredictability in the procedures for performing single or multiple site mutations and predicting the activity or function of the resulting protein, the present claims do not recite such procedures nor do the claims attempt to predict such results.

The present claims, as represented by Claim 47 for the protein PTP-1B, recite a method of identifying an exocite inhibitor of a PTP-1B (or TC-PTP) having phosphatase activity comprising a screening step, contacting the PTP-1B (or TC-PTP) with a test compound and determining the activity of the resulting protein. As described in the Examples, such procedures are routine, the level of unpredictability is low, and Applicants assert that the present application provides sufficient guidance, teaching and examples to enable the full scope of the claimed invention.

Guidance provided in the specification: As noted above, the specification teaches at least one hundred different specific structural permutations of PTP-1B and a large number of TC-PTP that may be employed in the method of the invention. In addition, the specification teaches the specific structures, amino acid residues, sequence alignments, amino acid variants in the adaptive binding site (paragraphs [0030] to [0031]) and specific interactions in the active site of the PTP domain (paragraphs [0021] to [0023], crystal structure of the residues for PTP-1B (paragraph [0032] and Figure 4), as well as the mechanism of hydrolysis, thus providing guidance as to the functional group requirements at the active site (paragraphs [0023] to [0024]). In addition, the specification provides examples of different inhibitors and methods of identifying the exosite inhibitors (paragraphs [0036] to [0041]) and throughout the specification. Furthermore, the specification provides detailed procedures for cloning PTP-1B and PTP-1B mutants, expression of cysteine mutants of PTP-1B, procedures for determining levels of inhibition and screening methods for potential exosite inhibitors. See paragraphs [0104] to [0116].

Accordingly, the specification provides sufficient, specific guidance with a number of examples for executing the claimed methods to teach one skilled in the art to experiment and practice the inventions.

Proper conclusion based on the analysis of the in re Wand factors

The above analysis demonstrates that Applicants provided a significant amount of guidance with concrete examples to enable one skilled in the art to practice the invention. The legal standard merely requires that "there must be sufficient disclosure, either through illustrative examples or terminology, to teach those of ordinary skill how to make and use the invention as broadly as it is claimed." *Enzo Biochem., Inc. v. Calgene, Inc., supra.* Furthermore, without a reason to doubt the truth of the statements made in the patent application, the application must be considered enabling. *In re Wright, supra*; *In re Marzocchi, supra.* Indeed, it is legally improper to limit the assessment of enablement to the actual working examples.

The CAFC has stated that "a considerable amount of experimentation is permissible, if it is merely routine, or if the specification in question provides a reasonable amount of guidance with respect to the direction in which the experimentation should proceed." See In *re Wands,Supra.* Here, the claims are definite and enabling because Applicants have taught both structure and function of the proteins, provide examples of protein variants, methods for their preparation and expression, and Applicants have clearly disclosed the use of the protein in the screening methods of the claimed invention.

And, in view of the art and the extensive and detailed teaching provided in the specification, Applicants respectfully submit that one of ordinary skill in the art would be able to practice the present invention as claimed. Although some experimentation might be necessary to prepare variants of PTP proteins and screen for their activities with test compounds, the procedures of which are within the scope of the pending claims, the fact

that such experimentation might be needed is not sufficient to establish that the experimentation is undue.

Because the Examiner has not provided specific reasons why Applicants did not provide a sufficient disclosure to enable the claimed invention, a *prima facie* case of lack of enablement has not been established, and the burden remains on the Examiner. Applicants respectfully request the Examiner to reconsider and withdraw the rejection of Claims 47-64, as amended, under 35 U.S.C § 112, first paragraph.

The 35 U.S.C. §102, Rejection:

[13] Claims 49 and 53-55 were rejected under 35 U.S.C. 102(b) as being anticipated by Wrobel *et al.* (J. Med. Chem. 42:3199-3202). According to the Examiner, the reference of Wrobel *et al.* teach a method for assaying the inhibitory activity of compounds against recombinant human PTP-1B by contacting the compounds against recombinant human PTP-1B in the presence of a phosphotyrosyl dodecapeptide, which anticipates Claims 49 and 53-55. The Examiner also noted that the recitation of the phrase "an exosite inhibitor of PTP-1B" in Claim 49 has not been given patentable weight because the recitation occurs in the preamble.

As amended, Claim 49 and therefore, its dependent Claims 53-55 presently recite that the PTP-1B is a protein that has the specifically recited amino acid residues that has phosphatase activity and comprising an exosite of PTP-1B, and accordingly, the test compound is one that is an exosite inhibitor of PTP-1B. Wrobel *et al.* do not teach nor suggest the method for assaying the inhibitory activity of compounds that are exosite inhibitors of PTP-1B nor that the protein is an exosite mutant of PTP-1B.

Accordingly, Wrobel *et al.* do not anticipate Claim 49 and its dependent Claims 53-55. Withdrawal of the 35 U.S.C. 102(b) rejection is respectfully requested.

[14] Claims 58 and 62-64 were rejected under 35 U.S.C. 102(a) as being anticipated by Asante-Appiah *et al.* (*J. Biol. Chem.* 276:26036-26043). According to the Examiner, Asante-Appiah *et al.* teach a method for assaying the inhibitory activity of compounds against recombinant human TC-PTP by contacting the compounds with recombinant human TC-PTP in the presence of various substrates. The Examiner also noted that Asante-Appiah *et al.* is silent as to the amino acid sequence of the recombinant human TC-PTP, but the polypeptide in Asante-Appiah *et al.* appears to be identical to the recombinant human TC-PTP in the specification. In addition, the Examiner noted that the recitation of the phrase "an exosite inhibitor of TC-PTP" in Claim 58 has not been given patentable weight because the recitation occurs in the preamble.

As amended, Claim 58 and therefore, its dependent Claims 62-64 presently recite that the TC-PTP is a protein that has the specifically recited amino acid residues having phosphatase activity and comprising an exosite of TC-PTP, and accordingly, the test compound is one that is an exosite inhibitor of TC-PTP. Asante-Appiah *et al.* do not teach nor suggest the method for assaying the inhibitory activity of compounds that are exosite inhibitors of TC-PTP having one or more of the recited amino acid residues, nor that the protein has phosphatase activity and comprising an exosite of TC-PTP.

Accordingly, Asante-Appiah *et al.* do not anticipate Claim 58 and its dependent Claims 62-64. Withdrawal of the 35 U.S.C. 102(a) rejection is respectfully requested.

Applicants respectfully submit that Claims 47-64, are in condition for allowance, and that allowance is respectfully solicited.

The present application is believed to be in *prima facie* condition for allowance, and an action to that effect is respectfully solicited. The Examiner is invited to contact the undersigned attorney at the telephone number below if the Examiner believe that there are any further outstanding issues.

Please charge any additional fees, including any fees for additional extension of time, or credit overpayment to Deposit Account No. **08-1641** (referencing Attorney Docket No. **39750-0008 C1**).

Respectfully submitted,

Date: August 11, 2006

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